

Applicant: Herbert T. Nagasawa et al.  
U.S. Serial No.: 10/750,005  
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**ADDITIONAL REFERENCES TO SUPPORT APPLICANTS' POSITION**

Applicants submit the following references to further support the arguments made in the Office Action response filed on July 11, 2007.

1. Hazelton, G.A. and Lang, C.A. (1980). Glutathione contents of tissues in the aging mouse. *Biochem. J.* 188, 25-30 (Exhibit 1).
2. Griffith, O.W. and Meister, A. (1979). Potent and specific inhibition of glutathione synthesis by buthionine sulfoximine (S-n-butyl homocysteine sulfoximine). *J. Biol. Chem.* 254, 7558-7560 (Exhibit 2).
3. Richman, P. and Meister, A. (1975). Regulation of gamma-glutamyl-L-cysteine synthetase by nonallosteric feedback inhibition by glutathione. *J. Biol. Chem.* 250, 1422-1426 (Exhibit 3).
4. Larsson, A. and Hagenfeldt, L. (1983). Hereditary Glutathione Synthetase Deficiency in Man. *Functions of Glutathione: Biochemical, Physiological, Toxicological, and Clinical Aspects*, Raven Press, New York (Exhibit 4).

The additional references cited, herein, support Applicants' position that there was no motivation to administer cysteine prodrugs to a subject nor was there a reasonable expectation of success that administering such cysteine prodrugs to a subject would provide the claimed results e.g., to reduce oxidative stress, to increase GSH levels or to reduce hepatotoxicity. The references support Applicants' position that merely because cysteine prodrugs (i.e. increasing cysteine levels in a cell) were known does not provide motivation or a reasonable expectation of success to achieve the claimed invention, because multiple factors interact to determine whether cysteine is converted into GSH in a cell (Office Action response dated July 11, 2007, at page 10, paragraph 4).

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For example, Hazelton and Lang, *supra*, confirm Applicants' position that "[a]s an organism ages, the GSH synthesis pathway becomes impaired leading to a decrease in GSH biosynthesis" (Office Action response dated July 11, 2007, at page 9, penultimate paragraph). Additional factors that may determine cysteine conversion into GSH include: the type of cell (Hazelton and Lang), the amount of cysteine present (Richman and Meister), feedback inhibition by GSH (Richman and Meister), blockage of the GSH synthesis pathway (Griffith and Meister) or impairment of the GSH synthesis pathway (Larsson and Hagenfeldt; Hazelton and Lang).

Cysteine is merely a molecule that along with glutamate can be, but is not necessarily, processed into GSH via a biosynthetic pathway. Therefore, there was no motivation to administer cysteine prodrugs to increase cysteine levels so as to produce the claimed invention. Also, even if cysteine prodrugs were administered and cysteine levels increased, there was no reasonable expectation of success of producing the claimed invention.

Accordingly, that an embodiment of the claimed sulfhydryl protected glutathione prodrug (e.g., CSSG) can release cysteine in addition to GSH is not relevant to the claimed invention. The advantage of the claimed invention is that sulfhydryl protected glutathione prodrugs such as CSSG can deliver preformed GSH to the cell whether or not cysteine is converted into GSH. Whether a molecule can increase cysteine is not pertinent to the claimed invention.

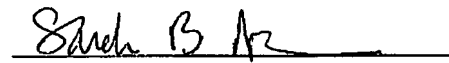
### CONCLUSION

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

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No fee, other than the \$120.00 one-month extension of time fee, is deemed necessary in connection with the filing of this Communication. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 50-0306.

Respectfully submitted,



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